COR ET VASA 55 (2013) E520–E524

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Review Article

What's new in the prevention of infective endocarditis?

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ARTICLE INFO

Article history:
Received 28 February 2013
Received in revised form
16 May 2013
Accepted 20 May 2013
Available online 28 May 2013

Keywords:
Infective endocarditis
Prevention of infective endocarditis
Prophylaxis prior to dental procedures
Staphylococcal endocarditis

ABSTRACT

The concept of prophylaxis of infective endocarditis has changed substantially in recent years; currently, prophylaxis is recommended only in patients at highest risk of developing infective endocarditis who are scheduled for dental procedures involving the gingiva. The risk is also increased in individuals with pacemakers and implantable cardioverter/defibrillators. Other high-risk populations include polymorbid patients (diabetes mellitus or chronic hemodialysis), the elderly (particularly those aged 75–79 years), and males. In indicated cases, the drugs used in prevention include amoxycillin or ampicillin.

Contents

Infective endocarditis (IE) belongs to the most serious diseases. In untreated patients, it is associated with 100% mortality, with in-hospital mortality being some 20% (despite the currently high standard of its diagnosis and treatment including cardiac surgery) [1,2]. While generally considered a rare disease, its incidence, though stable (also in the Czech Republic), is by no means negligible [3,4]. Data from a recent large French study show that IE occurs in 33.8 per 1 mil pop. [5]. The pattern of IE patients has also evolved, with elderly men now making up the largest patient population, as has the spectrum of causative agents (see below).

It follows from the above that the pivotal role in IE management is played by timely optimal therapy, with antibiotic prophylaxis, first proposed as early as 1955, being just an alternative approach [6]. Until recently, prophylaxis was indicated in patients at risk of developing IE while scheduled for a variety of procedures [7,8] involving the oral cavity, airways, cardiovascular system, gastrointestinal and urogenital tracts, and conditions including skin diseases and a wide range of congenital and acquired heart (primarily valve) diseases. However, the concept of IE prophylaxis has changed dramatically in recent years and the current list of

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http://dx.doi.org/10.1016/j.crvasa.2013.05.006

conditions requiring antibiotic prophylaxis has been critically revised and shortened.

It should be noted that the paradigm of IE prophylaxis was created and maintained on the basis of observational studies conducted in the early 20th century. The principal hypothesis was based on the assumption that bacteremia developing after a common procedure in at-risk patients may lead to the development of IE. There is also evidence that the bacteremia can be influenced by an antibiotic, as documented by experimental data [9]. While, essentially, these concepts have not become completely invalid since, a number of facts have emerged that actually make them somewhat obsolete. That was why the Task Force of the European Society of Clinical Microbiology and Infectious Disease and the International Society of Chemotherapy in Infections and Tumors jointly developed a document endorsed by the European Society of Cardiology addressing the issue of infective endocarditides [9]. The document markedly shortened the list of indications for antibiotic prophylaxis. Even more radical were the 2007 American Heart Association (AHA) guidelines [10,11] ruling out prophylaxis before gastrointestinal and urogenital procedures while recommending it only in patients at the highest risk of IE and scheduled for dental procedures. The most radical British (National Institute for Health and Clinical Excellence, NICE) guideline published a year later completely dismissed the concept of IE prophylaxis [12].

Recommendations for antibiotic prophylaxis most often apply to procedures in the oral cavity although there have also been occasional doubts whether or not streptococcal IE may actually develop via this pathway [13,14]; however, this possibility was documented by other studies [15]. In dental procedures involving the gingiva, and during everyday processes occurring in the mouth, bacteremia is present over a large range of 10–100% [16]; however, its impact on the development of IE is different in the completely healthy population and in individuals at risk of developing IE. In absolute numbers, the risk of IE in dental procedures is 1 per 14,000,000 in the general population while increasing dramatically to 1 per 95,000 in those with previous IE [17,18]. On the other hand, transient bacteremia will be detected during common processes occurring in the mouth such as tooth brushing and chewing [16,19]. Some data even suggest that everyday bacteremia occurs six million times more often than the bacteremia associated with single-tooth extraction [20]. In individuals with poor oral hygiene, bacteremia will develop independently of any procedures and everyday processes in the oral cavity [21]. In a large proportion of patients currently diagnosed with IE, bacteremia is not preceded by any clearly identifiable cause; hence, its source may be completely different from the suspected one [22]. Alternatively, is it possible that antibiotic prophylaxis is simply ineffective in new-onset IE treated with proper prophylaxis? Perhaps either possibility is partly true.

Moreover, antibiotic administration – particularly on a broader scale – is not devoid of risk. The spectrum of organisms resistant to certain antibiotics is expanding. Besides, antibiotic use is associated with the risk – albeit rather small – of anaphylaxis, and no lethal complication has been reported to date in connection with the administration of amoxycillin in the prevention of IE [23].

However, the main challenge in pharmacological prophylaxis of IE is that it has never been conclusively shown to be effective and the currently available results are fairly controversial. There is a complete lack of evidence showing that antibiotic-induced changes in the frequency or duration of bacteremia would impact the incidence of IE [9]. In the past, the typical IE patient was one with a predisposing valve disease who developed streptococcal endocarditis. However, this belief is no longer valid as IE has been shown not to be associated solely with a previous heart disease; moreover, its etiology in most patients is not streptococcal [2]. Still, it should be remembered that no large randomized controlled trial that could possibly provide a plausible answer has been conducted to date. An exception to this is the study by Lockhart and colleagues [16] investigating bacteremia in their 290 patients randomized into three groups: simple tooth brushing, tooth extraction with amoxicilin-based prophylaxis, or tooth extraction with placebo. Bacteremia was detected in 23% patients of the first group, 33% in the amoxicillin-based prophylaxis group, and in 60% of patients not receiving antibiotic prophylaxis. While, in light of all the above facts and studies, the earlier guidelines (including our past ones) [7,8] can obviously be considered obsolete, straightforward exclusion of antibiotic prophylaxis in the British NICE guideline [12] is unlikely to be a reasonable approach; based on our current knowledge, it just represents the other extreme which should not be adopted [9].

As formulated in the latest European guidelines, the prerequisites for IE prevention can be summarized in two main principles [9]: in IE prophylaxis, to focus attention on ***patients and procedures associated with the highest risk,*** and to maintain ***good oral hygiene***. The European guidelines are a well-balanced document, which puts the radical British guideline [9] disapproving any prophylaxis in opposition against the “rest of the world” [1].

As regards IE, **at-risk patients** can be divided into three categories [9].

(1) Individuals *with prosthetic valves* or any other prosthetic material employed for surgical correction of heart valve disease;
(2) Patients *with a history of IE*;
(3) Patients with *complex congenital heart disease*, cyanotic, not corrected surgically or those with residual shunts, implanted palliative shunts, conduits, or other types of prostheses. This category includes cases of congestive heart disease managed with a prosthetic material within 6 months (as endothelization is complete after 6 months and there is no longer any need for prophylaxis), persistent shunts following the implantation of the most varied types of materials using catheter-based or cardiac surgery procedures.

In the US guidelines, the third category includes heart transplant recipients developing valve dysfunction [11]; however, this indication is not supported by conclusive evidence. On the other hand, most cases of IE have recently been shown to occur in individuals without any pre-existing heart

disease [1,5]. The population at highest risk for developing IE are the elderly, with the incidence of IE peaking in the 75–79 age group (an up to tenfold increase in incidence), particularly among males [1,5]. It is also more frequent among polymorbid patients (with hypertension, diabetes mellitus, and those on chronic hemodialysis) [1].

Procedures carrying the risk of IE development [9].

These include, without any doubt, ***dental procedures*** involving manipulation the gingiva, periapical structures, and any injury to mucosal integrity (its perforation). This category does not include procedures involving the respiratory, gastrointestinal, or urogenital tracts, skin and soft tissue. In these cases, prophylaxis is not performed on a routine basis, except for high-risk patients undergoing a procedure where infection can reasonably be anticipated such as pulmonary abscess draining [9,19].

Some more recent studies [1] have suggested a ***pacemaker*** or an implantable cardioverter/defibrillator (ICD) may be associated with a higher risk for IE than originally believed. In a recent large multicentrer international prospective trial [24] following up 2760 patients, this type of IE was found in 177 individuals (more than 6%). The predominant type of infection was staphylococcal (*Staphylococcus aureus* in 35%, coagulase-negative staphylococcus in 32%). A most frequent finding was involvement of valve structures (particularly the tricuspid valve), with in-hospital and one-year mortality rates being close to 15% and 23%, respectively [24]. Significantly more favorable one-year mortality rates (20%) were reported for patients who had their whole system removed already during their first hospitalization compared with those who had not [24].

As suggested by a large prospective, randomized, placebo-controlled study, antibiotic prophylaxis may indeed confer protection to patients scheduled for implantation [25]. In this study, a total of 1000 implantation candidates were randomized to receive either prophylactic cefazolin or placebo infusion. The originally six-month study had to be stopped prematurely for significantly higher infection rates in the placebo arm; this outcome became reflected in the AHA guidelines, which were complemented with recommendation of prophylaxis before implant procedures [26]. At present, it is recommended to administer anti-staphyloccocal antibiotics, that is, first-generation cephalosporins (cefazolin) or vancomycin [1,26].

It should be emphasized in this context that there has been a steady rise in the rates of IE occurring in health care facilities (***health care-associated IE***), that is, nosocomial infections [2]. The typical microbes are both *Staphylococcus aureus* and coagulase-negative staphylococci described below and detected most often in elderly polymorbid patients (diabetes mellitus, hypertension, chronic hemodialysis) [1]. These patients do not necessarily include only those hospitalized but, also, outpatients (hemodialysis, intravenous chemotherapy). Some authors [27] have suggested this population represents up to 30% of IE cases and their prognosis is worse than that of patients with community-acquired IE [28].

High-risk microbes: They are primarily ***staphylococci*** causing over 36% of cases of IE [5]. The largest proportion of IE cases is caused by *Staphylococcus aureus* (26%) while the remaining 10% are caused by *coagulase-negative staphylococci* [5]. Staphylococcal infections tend to occur more frequently not only in addicts but, also, in hemodialysis and immunosuppressive-treated hospitalized patients scheduled for a variety of cardiac surgery procedures, implantation of pacemakers and similar devices; the proportion of individuals with a pre-existing heart disease in this population is usually smaller [29]. The frequent presence of these microbes in the etiology of IE led to the addition of *Staphylococcus aureus* as a typical microbe to the Durack criteria in 2000 [30]. The incidence of IE caused by *Staphylococcus aureus* rose from 5.2 cases in 1991 to 8.2 cases per one mil/pop. [1], with staphylococcal etiology considered one of the markers of a more serious prognosis [31]. As a result, procedures shown to be associated with the occurrence of this microbe (prosthetic valve and pacemaker implantation as well as chronic hemodialysis and diabetes mellitus) are potentially more challenging.

The issue of prosthetic staphylococcal IE was addressed in detail by a large multicenter international study [32] involving 537 patients with prosthetic valve endocarditis. Infective endocarditis caused by coagulase-negative staphylococci was detected in 16% of study participants, with half of them developing IE within 60–365 days after valve implantation. In a high proportion of cases (approx. 50%), IE was associated with abscess formation; IE caused by methicillin-resistant staphylococci was frequent (68%) [32]. In-hospital mortality related to coagulase-negative IE was 24% (36% with *Staphylococcus aureus* and 9% with viridans streptococci). A special case was recently reported with IE caused by *Staphylococcus lugdunensis* [33]. While rare, it is a form typically associated with extensive valve destruction and abscess formation, and poorly responding to antibiotic therapy [34].

According to the latest European guidelines, IE prophylaxis should only be performed in patients who are at highest risk and scheduled for dental procedures specified above [9].

The technique of IE prophylaxis is summarized in Table 1. All the listed antibiotics should be administered, at a single dose, 30–60 min preprocedurally [9]; the procedure is targeted

Table 1 – Prophylaxis in risk-related dental procedures [9].

	Single dose 30–60 min prior to procedure	
	Adults	Children
Amoxicillin or **ampilicilin**	2 g p.o. or i.v.	50 mg/kg p.o. or i.v.
Clindamycin*	600 mg p.o. or i.v.	20 mg/kg p.o. or i.v.

* Administered in patients with an allergy to penicillin or ampicillin.

primarily at oral streptococci. Antibiotic against staphylococci (oxacilin, vancomycin) can be used in disposed persons to cover procedures connected with pyogenic infection of skin and soft tissues.

As an exception, prophylaxis can also be undertaken in procedures other than the dental ones (see above). In such cases, it is recommended to use an antistaphylococcal penicillin or cephalosporin (e.g., in lung abscess draining, procedures involving skin abscesses or other purulent affections), vancomycin in MRSA, anti-enterococcal antibiotics in procedures involving the gastrointestinal tract (ampicillin, amoxycillin, vancomycin). Antibiotic prophylaxis is not mandatory in individuals at increased risk of IE who have piercing- or tattoo-related procedures as long as these are performed under strictly aseptic conditions [9]; however, this position may be revised (there have been case reports, albeit unconvincing, suggesting the potential for developing IE, e.g., after tongue piercing) [35].

Another quite serious and different issue is that related to patients presenting for valve replacement or implantation of a man-made material into the valve or blood vessels. These patients are at risk of developing early IE (within one year post-implant) caused by *Staphylococcus aureus* or coagulase-negative staphylococci. The recommendation is to perform prophylaxis immediately prior to the procedure; in the case of prolonged procedures, the antibiotic should be administered also post-operatively withdrawing it until 48 h after the procedure [9].

Is it possible to assess the impact of new guidelines on the incidence of IE in at-risk patients? This is a most intriguing question, although several hints have already emerged. Between 2000 and 2008, when the old guidelines were still in effect, there was a trend towards an increase in the number of cases of IE in the United Kingdom [36]. On the other hand, after the guidelines were substantially revised in 2008 dramatically reducing prophylactic prescription and use of antibiotics (with the British NICE guideline completely dismissing prophylaxis), the incidence of IE in the United Kingdom remained almost unchanged [36]. The French AEPEI (Association pour l'Etude et la Prévention de l'Endocardite Infectieuse) trial reported a similar phenomenon [1].

There is little doubt that the characteristics of IE as we know it today have changed substantially compared with what it was in the past. The disease affects increasingly more elderly individuals, primarily polymorbid patients with a variety of implanted devices [1]. In these individuals, antibiotic prophylaxis seems to be most appropriate [1]. Streptococci as the predominant causative agents have been replaced by staphylococci. It should always be remembered that most current guidelines are based on conclusions and consensuses of experts or on results of observational or experimental studies, while not actually incorporating data from evidence-based medicine. Hence, another revision of the guidelines should be reasonably expected, although one can only speculate about the extent of the changes [1,37].

In conclusion, it should be noted that concepts regarding IE prevention have witnessed substantial changes in recent years and “prevention is not as simple as in the good old days” [2]. The list of patients and procedures with recommended antibiotic prophylaxis has become shorter. Antibiotic prophylaxis is currently recommended only in patients at highest risk of developing infective endocarditis, that is, those scheduled to receive a prosthetic valve, patients with some types of complex congenital heart disease, implanted palliative shunts, conduits or prostheses as well as individuals with a history of IE. Those at highest risk include elderly and polymorbid patients (diabetes mellitus); the incidence of IE is currently not associated with a previous heart disease in most patients. Prophylaxis should be performed prior to dental procedures involving the gingiva and implantation of pacemakers and similar devices (ICD). Prophylaxis with amoxycillin or ampicillin at a dose of 2 g is administered 30–60 min preprocedurally; patients with allergy are given clindamycin whereas first-generation cephalosporins or vancomycin are used in patients scheduled for pacemaker or ICD implantation. Critical preventive measures in patients at high risk of IE include careful oral hygiene with regular dental checkups combined with maintenance of strictly sterile conditions during all risk-related procedures (pacemaker implantation and similar).

REFERENCES

[1] C. Chirouze, B. Hoen, X. Duval, Infective endocarditis prophylaxis: moving from dental prophylaxis to global prevention?, European Journal of Clinical Microbiology & Infectious Diseases 31 (2012) 2089–2095.

[2] A. Wang, The changing epidemiology of infective endocarditis. The paradox of prophylaxis in the current and future eras, Journal of American College of Cardiology 59 (2012) 1977–1978.

[3] J. Beneš, R. Baloun, O. Džupová, Endokarditidy 2007. Výsledky multicentrické studie o výskytu a vlastnostech infekční endokarditidy, Vnitřní Lékařství 57 (2011) 147–154.

[4] P. Gregor, Výskyt infekční endokarditidy a některé problémy její diagnostiky, Vnitřní Lékařství 57 (2011) 130–131.

[5] C. Selton-Suty, M. Celard, V. Moing, et al., Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey, Clinical Infectious Diseases 54 (2012) 1230–1239.

[6] American Heart Association, Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections, Circulation 11 (1955) 317–320.

[7] J. Beneš, P. Gregor, Infekční endokarditida, Triton, Praha182.

[8] J. Beneš, P. Gregor, A. Mokráček, Infekční endokarditida: doporučené postupy diagnostiky, léčby, dispenzarizace a profylaxe, Cor et Vasa 49 (2007) K157–K171.

[9] G. Habib, B. Hoen, P. Tornos, et al., Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009), European Heart Journal 30 (2009) 2369–2413.

[10] W. Wilson, K.A. Taubert, M. Gewitz, et al., Prevention of infective endocarditis: guidelines from the American Heart Association: Rheumatic fever, endocarditis, and Kawasaki disease Committee, Circulation 116 (2007) 1736–1754.

[11] R.A. Nishimura, B.A. Carabello, D.P. Faxon, et al., ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation 118 (2008) 887–896.

[12] National Institute for Health and Clinical Excellence (NICE), 2008. Prophylaxis against infective endocarditis (CG64). Antimicrobial prophylaxis against infective endocarditis. London , NICE, ⟨http://www.nice.org.uk/CG064⟩.

[13] J.T. Van Der Meer, W. Van Wijk, J. Thomson, et al., Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis, Lancet 339 (1992) 135–139.
[14] B.L. Strom, E. Abrutyn, J.A. Berlin, et al., Risk factors for infective endocarditis: oral hygiene and nondental exposures, Circulation 102 (2000) 2842–2848.
[15] F. Lacassin, B. Hoen, C. Leport, et al., Procedures associated with infective endocarditis in adults. A case control study, European Heart Journal 16 (1995) 1968–1974.
[16] P.B. Lockhart, The risk for endocarditis in dental practice, Periodontology 23 (2000) 127–135.
[17] J.M. Steckelberg, W.R. Wilson, Risk factors for infective endocarditis, Infectious Disease Clinics of North America 7 (1993) 9–19.
[18] T.J. Pallasch, Antibiotic prophylaxis: problems in paradise, Dental Clinics of North America 47 (2003) 665–679.
[19] A. Parrish, B. Maharaj, Prevention of infective endocarditis in developing countries—justifiable caution?, South African Medical Journal 102 (2012) 652–654.
[20] G.J. Roberts, Dentists are innocent! Everyday bacteremia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children, Pediatric Cardiology 20 (1999) 317–325.
[21] X. Duval, C. Leport, Prophylaxis of infective endocarditis: current tendencies, continuing controversies, Lancet Infectious Diseases 8 (2008) 225–232.
[22] H. Allen, Infective endocarditis: Updated guidelines, Canadian Journal of Infectious Diseases & Medical Microbiology 21 (2010) 205–212.
[23] X. Duval, F. Alla, B. Hoen, et al., Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis, Clinical Infectious Diseases 42 (2006) e102–e107.
[24] E. Athan, V.H. Chu, P. Tattevin, et al., Clinical characteristics and outcome of infective endocarditis involving implantable cardiac device, Journal of the American Medical Association 307 (2012) 1727–1735.
[25] J.C. de Oliveira, M. Martinelli, S.A. Nishioka, et al., Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial, Circulation: Arrhythmia and Electrophysiology 2 (2009) 29–34.
[26] L.M. Baddour, A.E. Epstein, C.C. Ericsson, et al., Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association, Circulation 121 (2010) 458–477.
[27] D.R. Mudroch, G.R. Corey, B. Hoen, et al., Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The International Collaboration on Endocarditis—Prospective Cohort Study, Archives of Internal Medicine 169 (2009) 463–473.
[28] N. Benito, J.M. Miro, E. de Lazzari, et al., Health care-associated native valve endocarditis: importance of non-nosocomial acquisition, Annals of Internal Medicine 150 (2009) 586–594.
[29] C.H. Cabell, J.G. Jollis, G.E. Peterson, et al., Changing patient characteristics and the effect on mortality in endocarditis, Archives of Internal Medicine 162 (2002) 633–638.
[30] J.S. Li, D.J. Sexton, N. Mick, et al., Proposed modifications to the Duke kriteria for the diagnosis of infective endocarditis, Clinical Infectious Diseases 30 (2000) 633–638.
[31] F. Thuny, R. Giorgi, R. Habachi, et al., Excess mortality and morbidity in patiens surviving infective endocarditis, American Heart Journal 164 (2012) 94–101.
[32] V.H. Chu, J.M. Miro, B. Hoen, et al., Coagulase-negative staphylococcal prosthetic valve endocarditis – a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study, Heart 95 (2009) 570–576.
[33] M. Sabe, N. Shrestha, S. Gordon, et al., Staphylococcus Lugdunensis: a rare but destructive cause of infective endocarditis with echocardiographic and clinical features similar to Staphylococcus Aureus infective endocarditis, Journal of American College of Cardiology 59 (2012) E2030.
[34] M. Ahmed, D. Sanghavi, A bug that bites a normal heart: case report and review of infective endocarditis by Staphylococcus Lugdunensis, Journal of American College of Cardiology 59 (2012) E2027.
[35] M. Yoshinaga, K. Niwa, A. Niwa, N., et al., Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease, American Journal of Cardiology 101 (2008) 114–118.
[36] M.H. Thornhill, M.J. Dayer, J.M. Forde, et al., Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study, British Medical Journal 342 (2011) 2392.
[37] X. Duval, F. Delahaye, F. Alla, et al., Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications. Three successive population-based surveys, Journal of American College of Cardiology 59 (2012) 1968–1976.